REMARKS

The specification has been amended to insert a brief description of new Figures 2 and 3 and to delete pages 10 and 11. This description includes sequence identifiers to the sequences found in Figures 2 and 3.

The specification on page 8 has been amended to insert sequence identifiers for the sequences found on page 8 and to correct the sequence of the mutated form of the preproNPY mRNA. The sequence of the mutated form of preproNPY is shown in Figure 1b and 1c. Thus, page 8 has been amended to conform to the mutated sequence shown in the Figures.

Claims 1-3 have been amended to change "subject" to "person" as suggested by the Examiner. Claim 3 has further been amended to delete reference to any cleavage product of preproNPY.

Claims 4-9 have been canceled as being drawn to non-elected inventions without prejudice to filing one or more division applications.

New claim 10 has been added to indicate that the polymorphism is detected by analysis of a nucleic acid encoding human preproNPY. Support for this amendment can be found at page 5, line 23 - page 6, line 7.

New Figures 2 and 3 have been added to replace Schemes 1 and 2 found on pages 10 and 11 of the specification.

A substitute Sequence Listing has been provided to include sequence identifiers to the sequences found in new Figures 2 and 3 and for the sequences found on page 8 of the specification.

It is submitted that none of the above amendments constitute new matter and their entry is requested.

The Examiner objected to claim 1 for improper antecedent basis for the term "subject." This term has been changed to "person" in accordance with the Examiner's suggestion in claims 1-3. This amendment obviates the objection, and its withdrawal is requested.

The Examiner objected to the specification for the inclusion of Schemes 1 and 2 on pages 10 and 11. These pages have been deleted by this amendment and replaced by new Figures 2 and 3. This amendment obviates this objection, and its withdrawal is requested.

The Examiner has rejected claims 1 and 3 under 35 U.S.C. § 112, first paragraph for lack of enablement. In essence, the Examiner contends that the specification does not enable methods for the detection of the polymorphism by the used of specific antibody or other polypeptide analysis. It is submitted that the Examiner is in error in this rejection.

The "examiner has the initial burden to establish a reasonable basis to question the enablement provided for the **claimed** invention." MPEP2164.04; *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed.Cir.1993) (emphasis added). In *Wright*, the Court made clear that the PTO has the burden of providing a reasonable explanation of why the specification does not enable. Furthermore, there must be some reason to doubt the objective truth of the statements in the specification. M.P.E.P. § 2164.04; *In re Marzocchi*, 169 USPQ 367 (CCPA 1973). Applicants submit that the Examiner has not provided acceptable evidence to doubt the objective enablement of the specification and to support her contention that the specification is not enabling. As the Court said in *Marzocchi*,

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis [i.e. doubt of the objective truth of statements in the specification] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go through the trouble and expense for supporting his presumptively accurate disclosure.

169 U.S.P.Q. at 370.

In addition, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known and already available to the public. M.P.E.P. § 2164.05(a). Applicants are not required to provide detailed information concerning matters which are known in the prior art and well within the ordinary skill of a practitioner such as the routine adjustment of dosage amounts. *See* M.P.E.P. § 2164.05(a).

Furthermore, contentions, without scientific reasons or evidence are not sufficient to sustain an enablement rejection. *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971). As provided in the M.P.E.P., if doubt arises about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation, the examiner "should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation." M.P.E.P., 2164.04. Furthermore, while references may not be required for the Examiner to meet his or her burden, "specific technical reasons are **always** required. *Id.* (emphasis added) To determine enablement, the specification is considered in light of the knowledge in the art at the time of the invention. When considering the adequacy of enablement for a generic claim, the M.P.E.P. states that proof of enablement is required for other members of the genus "...only where **adequate reasons** are advanced by the Examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." M.P.E.P. at 2164.02.

With respect to the analysis of the protein sequence of preproNPY, it is submitted that the isolation and sequencing of proteins was well known in the art at the filing date of the present application. The mere absence of exemplified methods is not a suitable basis for lack of enablement. In re Wands, (Fed Cir,). The Examiner has not provided any specific technical reasons to doubt the objective enablement of the specification or to demonstrate that **undue** experimentation would be required to practice the claimed subject matter. Thus, Applicants submit that the detection of the specified polymorphism by protein analysis is fully enabled by the specification.

With respect to antibody, the Examiner contends that enablement is lacking because the specification has not shown any antibody capable of differentiating the wildtype and mutant proteins and because of the phenomenon of "cross-reactivity." Applicants submit that the specification fully enables the preparation of an antibody for use in the method. Specifically, Applicants submit that it would not require undue experimentation to identify and develop monoclonal antibodies against the epitopes of an altered (i.e., mutated) preproNPY, in light of the high level of skill in the art. This

process involves well-documented techniques in immunization, hybridoma cell fusion technology, and antibody screening strategies, to generate and select monoclonal antibodies that can serve as immunological probes with highly defined specificities. Indeed, in the literature over more than a decade, monoclonal antibodies have been described that can differentiate between minute changes in molecular structure, including single amino acid differences in proteins, oxidation states of lipids, stereoisomers and post-translational modification of identical gene products, even down to a single glucose molecule. As noted above, such techniques, known to skilled artisans, do not need to be described in the specification. Since undue experimentation would not be required to produce an appropriate antibody, it is submitted that the fact that the specification does not show such an antibody is not a technical reason to support the Examiner's position of non-enablement.

In addition, the phenomenon of "cross-reactivity" does not present a sufficient technical reason to establish that the specification is not enabling. As pointed out by the Examiner, the phenomenon of "cross-reactivity" is well-known in the antibody art, and it is also well known that any given antibody to a polypeptide may or may not exhibit cross-reactivity. Thus, a skilled artisan knows that an antibody must be tested for cross-reactivity if it is desired to identify an antibody which binds specifically to a particular epitope. It is well known that a skilled artisan determines cross-reactivity by screening antibodies. It is submitted that such screening of antibodies for cross-reactivity, a technique conventionally performed by skilled artisans, does not represent undue experimentation. Furthermore, it is submitted that the Examiner has not provided any reasoning to suggest that such screening would be undue experimentation. Since undue experimentation is not required, it is submitted that the phenomenon of "cross-reactivity" does not provide a technical reason to support the Examiner's position of non-enablement.

With respect to "other cleavage product of preproNPY," claim 3 has been amended to delete this language. The deletion of this language removes one basis for the rejection of claim 3 for lack of enablement.

In view of the above amendments and remarks, it is submitted that the claims comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of this rejection is requested.

The Examiner has rejected claim 3 under 35 U.S.C. § 112, second paragraph for being indefinite. It is submitted that the amendment of claim 3 obviates this rejection, and its withdrawal is requested.

In view of the above amendments and remarks, it is submitted that the claims satisfy the requirements of the patent statutes and are patentable over the prior art. Reconsideration of the instant application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

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Attachments: New Figures 2 and 3
Substitute Sequence Listing

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AMENDMENTS TO THE DRAWINGS

The attached two sheets of drawing include new Figures 2 and 3. These Figures correspond to Scheme1 and Scheme 2, respectively, as originally found on pages 10 and 11 of the specification with the following changes.

Figures 2 and 3 do not include the entire nucleotide sequence as found in Schemes 1 and 2, but only a part of the sequence, especially the part surrounding the polymorphism in the signal peptide portion of preproNPY. The entire nucleotide sequence is set forth in Figure 1c. In addition, the "t" found in the string of nucleotides in Scheme 1 has been changed to "u" in Figure 2. This change is supported in the description of Scheme1, as originally found on page 10 of the specification as filed which states that the scheme shows preproNPY mRNA. The "u" is present in mRNA, not "t" which is present in DNA.

Attachment: New Sheets of Figures 2 and 3

SEQUENCE LISTING

Please substitute the attached 4 pages of Sequence Listing submitted herewith for the 3 pages of the Sequence Listing of the published PCT application. The sequence listing has been modified to set forth the present application information and to add the sequences of new Figures 2 and 3 and found in the specification on page 8. It is certified that the sequence listing includes no new matter. Entry of this sequence listing is requested. A computer readable form and an 821(f) Statement accompany this Amendment.